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Ifosfamide Nephrotoxicity in Children: Histopathological Features in Two Cases

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We report on two children with rhabdomyosarcoma who received ifosfamide as part of their chemotherapy schedule. Both children subsequently developed severe ifosfamide-induced nephrotoxicity, necessitating electrolyte supplementation. We describe the histopathological findings of renal biopsies performed in these children after the onset of renal dysfunction and comment on the possible mechanisms involved in ifosfamide nephrotoxicity.

Key words: ifosfamide, nephrotoxicity, histopathology, renal biopsy

INTRODUCTION

The alkylating drug ifosfamide is currently used as first-line chemotherapy in a wide range of paediatric malignancies (Ewing's sarcoma, rhabdomyosarcoma, Wilms' tumour, neuroblastoma, and lymphoma). The biochemical disturbances associated with ifosfamide nephrotoxicity are well described [1] and are a consequence of glomerular or tubular toxicity. Glomerular damage causes nonspecific proteinuria and a fall in glomerular filtration rate (GFR). The tubular defects lead to increased urinary losses of glucose, amino acids, phosphate, bicarbonate, retinol binding protein, α_1-microglobulin, and β_2-microglobulin [2].

It is difficult to predict the risk of nephrotoxicity to individual patients [3]; however, it has been suggested that younger children (<5 years) [4], and those receiving a total cumulative dose of ifosfamide of >60 gm^2 [2] prior to [5] or concurrent with [6] cisplatin therapy, and children with pre-existing renal impairment [7], are more likely to develop problems. Once ifosfamide has been given to patients, it is possible to evaluate subclinical renal toxicity, and this may have predictive value for the likelihood of subsequent chronic toxicity [8]. The reversibility of ifosfamide nephrotoxicity is similarly difficult to predict. There is usually the appearance of subclinical tubular or glomerular damage detectable only by appropriate laboratory investigations, but serious and irreversible tubular and glomerular damage may occur in a small proportion of children. These show a progressive fall in glomerular filtration rate during therapy, and this may continue after withdrawal of the drug. Fanconi syndrome may appear later, causing rickets and growth failure.

The histological features of ifosfamide nephrotoxicity have been previously described in four patients [9–12], two of which were children. We report two further cases of severe ifosfamide nephrotoxicity in children and describe the histological features seen in renal biopsies from them.

CASE REPORTS

Case 1

A 5-year-old boy presented with a 3 month history of nasal discharge, nasal blockage, halitosis, and altered speech quality. Referral had been precipitated by the appearance of a polypoid mass arising from the left nostril. Tissue obtained during subsequent debulking of the posterior nasal space demonstrated the presence of an embryonal rhabdomyosarcoma.

No metastases were found on subsequent radiological stating. The tumour was classified as a parameningeal stage II pT3b rhabdomyosarcoma. Chemotherapy (ifosfamide, vincristine, and actinomycin D [IVA]) was started according to the SIOP MMT-89 study, and between August 1991 and January 1992 the boy received six blocks of treatment with a cumulative ifosfamide dose of 54 g/m^2. He also received a course of radiotherapy to the posterior nasal space (45 Gy in 25 fractions). During treatment there was no significant rise in serum creatinine, and GFR measured by ^{51}CrEDTA clearance after a

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cumulative dose of 36 g/m^2 of ifosfamide was 90 ml/min/1.73 m^2. Two months after completion of therapy, serum phosphate had fallen to 0.76 mmol/l. Alkaline phosphatase was 631 U/1, early morning urine osmolality was 525 mOsmol/kg, but GFR was unchanged at 90 ml/min/1.73 m^2. Wrist x-ray demonstrated features consistent with rickets, and the child was commenced on phosphate supplements.

Three months later, despite continued phosphate supplements, serum phosphate remained subnormal at 0.72 mmol/l and serum parathyroid hormone levels were elevated at 81 ng/l (normal range 10–40 ng/l). Further evidence of tubular damage was suggested by a raised early morning urinary protein/creatinine ratio of 317 mg/mmol (normal <20 mg/mmol).

Deterioration in renal function continued up to 1 year following cessation of therapy. GFR subsequently fell to 56 ml/min/1.73 m^2, early morning urine osmolality to 452 mOsmol/kg, urine protein/creatinine ration to 700 mg/mmol, serum phosphate to 0.96 mmol/l, serum bicarbonate to 17.5 mmol/l, serum potassium 3.0 mmol/l, and renal threshold for phosphate (Tm_p/GFR) to 0.16 mmol/l (normal $\geq$1.0). A mannitol infusion test [13] was carried out that demonstrated a combined proximal and distal tubular defect to be present. Renal biopsy was undertaken and the histological features are reviewed later. The patient remains alive 40 months from diagnosis, with no evidence of tumour recurrence. He remains on phosphate, potassium, and bicarbonate supplements, and renal function is stable.

Case 2

A 5-year-old girl was referred following biopsy of a swelling that had been present on her chin and increasing slowly in size for 6 months. The biopsy confirmed an embryonal rhabdomyosarcoma. There was histological confirmation of submental lymph node involvement but no other spread of tumour. She was commenced on the SIOP MMT 89 protocol. Between April 1991 and February 1992, she received combined drug chemotherapy (carboplatin, epirubicin, ifosfamide, etoposide, actinomycin D, and vincristine) with a cumulative dose of ifosfamide of 57 g/m^2 and radiotherapy (45Gy) to the site of the primary tumour.

Seven months after chemotherapy had finished, the patient required potassium and phosphate supplements. At this stage serum creatinine was slightly elevated at 80 μmol/l. One year following cessation of treatment, ^{51}CrEDTA slope clearance revealed a GFR of 51 ml/min/1.73 m^2, serum phosphate was .82 mmol/l, early morning urinary osmolality was 205 mOsmol/l, urine protein/creatinine ratio was 421 mg/mmol, and retinol binding protein was 46 (normal <10). Renal biopsy was performed and the histological findings are described later. Forty-two months from diagnosis, Albright's solution (citric acid 33 g, sodium citrate 25 g, potassium citrate 25 g diluted to 500 ml with distilled water) was added to her therapy because of intermittently low serum total CO_2 levels and because of poor linear growth.

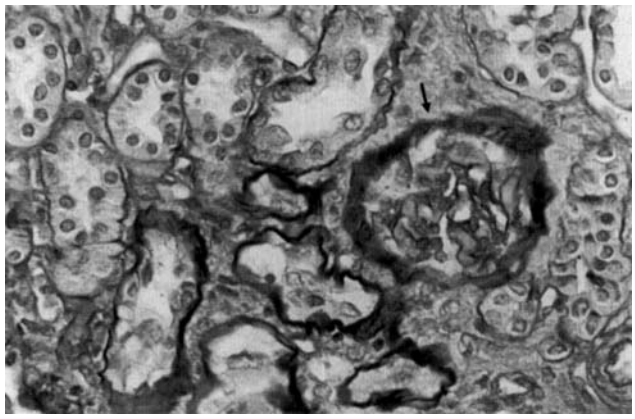

Fig. 1. Case 1. Tubular atrophy represented by wrinkling of the basement membrane. There is also some wrinkling of Bowmans' capsule (PAS, ×780).

Forty-five months from diagnosis, the child is alive with no evidence of tumour recurrence. She is still receiving additional potassium, phosphate, and Albright's solution supplements. Her GFR is stable at 61 ml/min/1.73 m^2.

Table I (after Skinner et al. [1]) summarises four of the parameters of nephrotoxicity demonstrated in the two case reports (case 1 at 2 ½ years from diagnosis; case 2 at 2 years from diagnosis). Each parameter of toxicity is graded 0–4 depending on severity and an overall estimation of renal damage provided by the sum of all individual gradings such that 0 = no toxicity, 1–3 = mild nephrotoxicity, 4–7 = moderate toxicity, and 8 = severe toxicity. Both cases presented therefore demonstrate severe nephrotoxicity.

HISTOPATHOLOGY OF RENAL BIOPSIES

Case 1

The biopsy taken 14 months from cessation of chemotherapy showed severe focal tubulointerstitial damage, represented by tubular atrophy (Fig. 1) and interstitial infiltration by lymphocytes and plasma cells. Occasional tubules showed hyperplastic binucleate epithelial lining cells and were infiltrated by lymphocytes (emperipolesis). Glomeruli were well preserved, as were the arteries and arterioles. Electron microscopy was performed on glomeruli only and showed no abnormality.

Case 2

The biopsy taken 15 months from cessation of chemotherapy showed tubular atrophy and segmental sclerosis

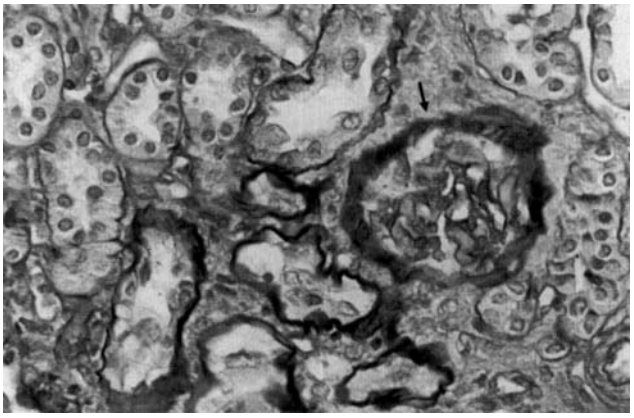

Fig. 2. Case 2. High power view of an area of tubular atrophy with periglomerular wrinkling of Bowman's capsule (arrow) (H&E ×480).

of one glomerular tuft with slight mesangial expansion of another (Fig. 2). Except for one area of inflammation at the cortico-medullary junction, the interstitial tissue was well preserved.

DISCUSSION

We report the pathological changes seen in the renal biopsies of two children with ifosfamide-induced nephrotoxicity. Both children have evidence of severe nephrotoxicity, as determined by the biochemical parameters outlined in Table I, using the grading system of Skinner et al. [1]. Despite a similar clinical pattern of tubular and glomerular damage, the histopathological findings between these children varied considerably. This variability is also evident from the previously reported cases of renal biopsies from patients with ifosfamide nephrotoxicity outlined in Table II.

The acute tubular damage induced by ifosfamide may be due to the drug itself or the production of toxic metabolites. In their comprehensive review of ifosfamide nephrotoxicity in children, Skinner et al. [1] put forward the hypothesis that one of the most likely candidates for inducing renal cellular damage was the metabolite chloroacetaldehyde. It is known that this metabolite is highly toxic to epithelial cells, which may explain the histological pattern of tubular atrophy seen in previous reports and by ourselves (Table II).

Ifosfamide toxicity can be manifest at the level of the glomerulus, tubules, or interstitium. The glomerular lesion is characterised by segmental sclerosis, often with focal tubular atrophy. The tubular damage, which is more common, manifests as tubular necrosis and inflammation with lymphocytic infiltration of tubules, not unlike the acute tubulointerstitial rejection associated with renal transplantation. The proximal tubules are more often involved, but the nephron can be affected at any level. The exact mechanism underlying the tubular toxicity is unclear, but the rich blood supply and high metabolic rate of proximal tubule cells make them particularly susceptible to toxic insults. The tubular damage, which is initially limited to the cells lining the tubules, may extend to the basement membrane and so impede recovery, depending on the extent and duration of exposure to the injurious agent.

Along with evidence of toxic tubular damage, an element of interstitial nephritis would seem to be part of the spectrum of ifosfamide-induced nephropathy, as seen in our case 1 and in that of Jenney et al. Such features are recognised in other drug-induced nephropathies, such as methicillin, ampicillin, cephalosporins, and others [14]. Interstitial nephritis is represented by lymphocyte and plasma cell infiltration as a consequence of tubular necrosis. The histopathology is quite distinct from chronic pyelonephritis, where the inflammatory cells with lymphoid follicle formation are focal.

We suggest the following hypothesis to explain the histological appearances of ifosfamide nephrotoxicity. The toxic agent(s) filter through to the tubules, where the epithelial lining is damaged through direct toxic action. This results in tubular necrosis and secondary inflammatory cell reaction. If the tubular cell damage is extensive and occurs repeatedly, it may lead to basement membrane necrosis, which probably reaches a "point of no return" as far as tubular regeneration is concerned.

As mentioned previously, the extreme variability in histopathological findings in ifosfamide nephrotoxicity cannot be emphasised too greatly. The timing of the biopsy may be an important factor. Unfortunately from the previously reported cases, it is only clear from two cases as to the timing of biopsy in relation to therapy. In the cases reported by Willemse et al. and Devalk et al., both patients were biopsied "early", either during or very near to the completion of ifosfamide therapy. This is in contrast to our patients, in whom biopsies were obtained over a year from the end of treatment. The "early" biopsies would support the hypothesis that direct tubular insult may be the first damaging event, and it is interesting to note that inflammatory infiltrates were not a feature of these biopsies. In contrast, the inflammatory nephritis seen in one of our cases may represent a later feature of ifosfamide nephrotoxicity. Once this inflammatory reaction has been induced by direct toxic tubular damage, it may itself result in a self-perpetuating process by inducing further tubular damage. This may in part be responsible for the chronicity of renal impairment seen in some patients.

As yet little evidence exists to suggest that the pathological changes observed in ifosfamide-induced nephrotoxicity alter with time. Despite this it is interesting to speculate that, as with some other drug-induced nephropathies, the nephrotoxicity may be reversed by withdrawal

TABLE I. Summary of Nephrotoxicity in the Two Cases Reported

Parameter of nephrotoxicity	Case 1		Case 2	
	Value	Grade	Value	Grade
GFR	56	2	51	2
Tm_p/GFR (normal ≥1.0)	0.16	4	0.46	4
HCO_3	14.0	2	>20	0
EMUO	452	2	205	4

GFR determined by Cr^{51}EDTA clearance (ml/min/1.73m^2), Tm_p/GFR (mmol/l) = $P_p - ([U_p \times P_{cr}]/U_{cr})$, where P = plasma concentration, p = phosphate, U = urine concentration, and cr = creatinine. HCO_3 = serum bicarbonate (mmol/l); EMUO = early morning urine osmolality (mosmol/l).
Data from Skinner et al. [1].

TABLE II. Previous Case Reports of Pathological Changes Observed in Ifosfamide-Induced Nephrotoxicity

Report	Age	Cumulative ifosfamide dose	Other chemotherapy	GFR	Histology
Jenney et al. [9]	2	Not stated	None	34	Pronounced tubular atrophy and a severe tubulointerstitial nephritis
Willemse et al. [10]	62	20 g/m^2	Prior therapy with cisplatin	2–3	Hyalinization of 8/13 evaluable glomeruli; focal tubular atrophy and interstitial fibrosis with some lymphocytic infiltration; diffuse interstitial fibrosis; no interstitial nephritis or tubular necrosis
Devalk et al. [11]	Child	13.5 g/m^2	None	NS	Focal proximal tubular sclerosis compatible with a toxic tubulopathy
Rossi et al. [12]	24	80 g/m^2	Combined therapy with cisplatin	75	Focal proximal tubule defects; 60% of cortical tubules showing partial loss of epithelial cells with denudation of adjacent basement membrane
Present report	7	54 g/m^2	None	56	See text
	7	57 g/m^2	None	51	

of the offending drug and by the use of corticosteroid therapy. We did not use steroid therapy in any of our patients and can only speculate on its possible effect in ifosfamide-induced nephrotoxicity.

There is a need to accumulate further information on the pathology of ifosfamide nephrotoxicity. More reports would be welcomed, particularly emphasising the timing of biopsy in relation to ifosfamide treatment. The evolving pattern of renal damage within individual patients would be of particular interest; however, the ethics of repeat renal biopsy in patients in whom there are no significant changes in clinical parameters is difficult to address. The analysis of renal biopsy material obtained post mortem from patients dying from disease recurrence may be one way of obtaining this information.

It may be important to identify risk factors in advance of giving potentially nephrotoxic chemotherapy, but in our two reported cases none of the recognised risk factors (age, cumulative dose of ifosfamide, other nephrotoxic drugs) would seem to apply. This further reinforces the need for close monitoring of all patients and highlights the variability between individuals receiving similar treatments. It is difficult to predict the outcome for the children discussed, but whereas the probability of long-term cure from rhabdomyosarcoma remains high, there are very few reports to suggest that this level of nephrotoxicity is reversible in the majority of children [8,15,16]. The risk of continued tubular dysfunction and the development of end-stage renal failure must be a possibility.

These findings stress the importance of close monitoring and long-term follow-up of survivors of childhood malignancy. Absolute survival is only one measure of success, and paediatric oncologists are now increasingly aware of the importance of the quality of life of children cured of cancer [17].

REFERENCES

1. Skinner R, Sharkey IM, Pearson ADJ, Craft AW: Ifosfamide, mesna and nephrotoxicity in children. J Clin Oncol 11:173–190, 1993.
2. Skinner R, Pearson ADJ, Price L, Coulthard MG, Craft AW: Nephrotoxicity after ifosfamide. Arch Dis Child 65:732–738, 1990.
3. Stevens MCG, Brandis M: Incidence and etiology of ifosfamide nephrotoxicity: Report of a meeting held at Rhodes, Greece, October 3, 1991, sponsored by Asta Medica, Frankfurt, Germany. Med Pediatr Oncol 21:640–644, 1993.

4. Skinner R, Pearson ADJ, Price L, Coulthard MG, Craft AW: The influence of age on nephrotoxicity following chemotherapy in children. Br J Cancer 66(Suppl 18):S30–S35, 1992.
5. Moncrieff M, Foot A: Fanconi's syndrome after ifosfamide. Cancer Chemother Pharmacol 23:121–122, 1989.
6. Caron HN, Abeling N, van Gennip A, de Kraker J, Voûte PA: Hyperaminoaciduria identifies patients at risk of developing renal tubular toxicity associated with ifosfamide and platinate containing regimens. Med Pediatr Oncol 20:42–47, 1992.
7. Davies SM, Pearson ADJ, Craft AW: Toxicity of high-dose ifosfamide in children. Cancer Chemother Pharmacol 24(Suppl):S8–S10, 1989.
8. Skinner R, Pearson ADJ, Price L, Wyllie RA, English MW, Hodson AW, Skillen AW, Coulthard MG, Craft AW: Ifosfamide nephrotoxicity in children: Early detection and prediction of severity. Med Pediatr Oncol 23:178, 1994.
9. Jenney M, Morris-Jones P, Gattamaneni HR, Lewis MA: Ifosfamide for children with solid tumours (letter). Lancet 1:1398, 1990.
10. Willemse PHB, de Jong PE, Elema JD, Mulder NH: Severe renal failure following high-dose ifosfamide and mesna. Cancer Chemother Pharmacol 23:329–330, 1989.
11. Devalck C, Ismaili K, Ferster A, Sariban E: Acute ifosfamide-induced proximal tubular toxic reaction (letter). J Pediatr 118: 325–326, 1991.
12. Rossi R, Helmchen U, Schellong G. Tubular function and histological findings in ifosfamide-induced renal Fanconi syndrome—a report of two cases. Eur J Pediatr 151:384–387, 1992.
13. Oetliker OH, Simon J, Tietze HU: Diagnostic value of mannitol-induced diuresis in children. Acta Scand Pediatr 63:113–121, 1974.
14. Koren G: The nephrotoxic potential of drugs and chemicals. Pharmacological basis and clinical relevance. Med Toxicol Adverse Drug Exp 4:59–72, 1989.
15. Suarez A, McDowell H, Naiudet P, Comoy E, Flammant F: Long-term follow-up of ifosfamide renal toxicity in children treated for malignant mesenchymal tumors: An International Society of Pediatric Oncology report. J Clin Oncol 9:2177–2182, 1991.
16. Rossi R, Rath B, Deulfel T, Riepenhausen M, Jürgens H: Ifosfamide nephrotoxicity: Frequency and prognosis of severe tubular damage (abst). Pediatr Nephrol 8:C42, 1994.
17. Pinkerton CR: Avoiding chemotherapy related late effects in children with curable tumours. Arch Dis Child 67:1116–1119, 1992.